

BIOGRAPHICAL SKETCH

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NAME: **Lily Q. Dong**

eRA COMMONS USER NAME: **DONGLQ**

POSITION TITLE: **Professor**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Wuhan University, Wuhan, China	B.S.	7/1982	Biochemistry
Wuhan University, Wuhan, China	M.S.	7/1985	Biochemistry
Iowa State University, Ames, Iowa, US	Ph.D.	5/1991	Biochemistry
Stanford University, Stanford, California, US	Post-doctoral	11/1995	Molecular Biology

A. PERSONAL STATEMENT

I have devoted my research career to studying the fundamental mechanisms underlying insulin resistance and its related diseases including obesity and type 2 diabetes with special emphasis on adiponectin signaling and the cross talk between adiponectin and insulin signal pathways. As a Principal Investigator, I have a record of continuous funding from NIH, American Diabetes Association, American Heart Association and private foundations. I have extensive and successful experience in developing and administering new research projects, motivating students and postdoctoral fellows, collaborating with other researchers, and producing high-quality publications. Thus, I have a demonstrated track record of success and productivity in the diabetes research field.

During the past fifteen years, I have mentored a large number of young scientists including high school students, college undergraduates, graduate students, post-doctoral fellows and junior faculty. I have received several teaching and educational awards at various levels including Departmental, University-Wide and Texas Board of Regents. Based on my long-standing commitment to training next generation scientists, the scientific impact of our research, and the strong connection with Biomedical research field, I believe that I am particularly well suited to my role as a mentor for students in the Xiangya Medical Student Research Program.

Representative publications:

1. Lim, M. A., Kikani, C. K., Wick, M. J., and **Dong, L. Q.** (2003). Nuclear translocation of 3'-phosphoinositide-dependent kinase-1: a potential regulatory mechanism for PDK-1 function. Proc. Natl. Acad. Sci. USA. 100, 14006-14011. PMID:14623982.
2. Mao, X., Kikani, C. K., Riojas, R. A., Langlais, P., Wang, L., Ramos, F. J., Fang, Q., Christ-Roberts, C.Y., Hong, J.Y., Kim, R. Y., Liu, F., and **Dong, L. Q.** (2006). APPL1 binds to adiponectin receptors and mediates adiponectin signaling and function. Nature Cell Biology. 8, 516-523. **(Highlighted article on cover page)**
Featured in commentary article: Lin, D.C. et al., (2006) APPL1 mechanics: uncovering how adiponectin modulates insulin action. Cell Metabolism. 4, 5-6.
3. Ryu, J., Galan, A.K., Xin, X., Dong, F., Abdul-Ghani, M.A., Zhou, L., Wang, C., Li, C., Holmes, B.M., Sloane, L.B., Austad, S.N., Guo, S., Musi, N., DeFronzo, R.A., Deng, C., White, M.F., Liu, F., and **Dong, L.Q.** (2014) APPL1 Potentiates Insulin Sensitivity by Facilitating the Binding of IRS1/2 to the Insulin Receptor. Cell Reports, 7, 1227-1238.

B. POSITIONS AND HONORS

Positions and Employment:

1996 - 1998	Instructor (Research), Department of Pharmacology, University of Texas Health Science Center at San Antonio (UTHSCSA)
1998 - 2002	Assistant Professor (Research), Department of Pharmacology, UTHSCSA
2002 - 2007	Assistant Professor (Tenure-Track), Department of Cellular & Structural Biology (Primary appointment), Department of Pharmacology (Cross-appointment), UTHSCSA
2007 - 2011	Associate Professor (with Tenure), Department of Cellular & Structural Biology (Primary appointment), Department of Pharmacology (Cross-appointment), UTHSCSA
2011 - 2016	Professor (with Tenure), Department of Cellular & Structural Biology (Primary appointment) (Renamed to Department of Cell Systems & Anatomy in 2016), Department of Pharmacology (Cross-appointment), UTHSCSA (Renamed to UTHSA in 2016)
2016 – present	Professor (with Tenure), Department of Cell Systems & Anatomy (Primary appointment), Department of Pharmacology (Cross-appointment), University of Texas Health San Antonio (UTHSA)

Professional Societies and Committees:

NIH/NIDDK/CADO Study Section, Ad hoc member (2005-Oct)
NIH/NHLBI PPG Special Panel, Member (2007 and 2010)
NIH/ Director's Early Independence Award (2015), a mail Reviewer
NIH/NIDDK/ ZDK1 GRB-W (J1) Special Panel, Member (2009 - 2011)
NIH/NIDDK/IPOD Study Section, Ad hoc member (Feb. 2008; Oct. 2015; Feb. 2016)
NIH/NIDDK/IPOD Study Section, Standing member (July-2016 to present)

American Heart Association Grant Review Panel (Committee: Western 3A), Member (2005 - 2009)
American Federation for Aging Research (AFAR)'s National Scientific Advisory Council, Member (2008 – present)
American Diabetes Association Scientific Sessions Topic Planning-Insulin Signaling/Insulin Action Subcommittee (2010)
American Diabetes Scientific Sessions Association abstract and Late Breaking Abstract Reviewer (2012)
American Diabetics Association Research Grant Review Committee, Member (2011 - present)

Diabetes UK, External Reviewer (2008 – present)
Hong Kong Earmarked Research Grant (ERG), External Reviewer (2009 - present)
The Research Grants Council (RGC) of Hong Kong, External Reviewer (2010 - present)
National Research Foundation of Korea, External Reviewer (2013 - present)
National Science Foundation of China (NSFC) (2010-2013) (2016)
Israel Science Foundation (ISF) (2015 - present)

Editorial board member: *Adipocyte* (2011- present)
Associate Editor: *Reviews in Endocrine & Metabolism Disorders* (2012 - 2014)
Editorial board member: *J. Biol. Chem.* (2013 - present)

American Society for Pharmacology and Experimental Therapeutics, Member (2001 – present)
San Antonio Cancer Institute, Associate Member (2000 - present)
The Endocrine Society, Member (2000 - 2009)
American Diabetes Association, Member (2002 – present)

Awards and Honors:

1991 Graduate Student Research Award (Department of Biochemistry & Biophysics, Iowa State University).
1998 American Heart Association Research Award (Texas Affiliate)
2003 American Heart Association Research Award (Texas Affiliate); New Faculty Startup Award (HHMI-UTHSCSA); Junior Faculty Development Award; South Texas Health Research Center (UTHSCSA)
2005 American Diabetes Association (Career Development Award); Travel Award (American Diabetes Association);
2008 Award for Excellent in Graduate Student Education (Department of Cellular & Structural Biology, UTHSCSA)
2010 Named as Master Teacher and Distinguished Teaching Professor by the University of Texas Health Science Center at San Antonio.
2013 Presidential Teaching Excellent Award (UTHSCSA)

C. CONTRIBUTION TO SCIENCE

- 1) **Insulin signal transduction:** I have more than twenty years' experience in the field of insulin signaling, insulin resistance and type 2 diabetes researches. I have a solid training in biochemistry, molecular biology, signal transduction, and metabolism. As a junior faculty, I started working on the mechanism of insulin resistance and type 2 diabetes, mainly focusing on two key molecules (**Grb10 and PDK1**) in insulin signaling pathway. I have published more than fifteen papers during this time, which clearly demonstrated that Grb10 is a negative regulator of insulin and IGF-1 signaling and action, and the molecular mechanism of PDK1 action in the PI3 kinase pathway.
- a) **Dong, L. Q.**, Farris, S., Cristal, J. and Liu, F. (1997) Site-directed mutagenesis and yeast two-hybrid studies of the insulin and insulin-like growth factor-1 receptors: The SH2 domain-containing protein hGrb10 binds to the autophosphorylated tyrosine residues in the kinase domain of the insulin receptor. *Mol. Endo.* 11, 1757-1765.
 - b) **Dong, L. Q.**, Farris, S., Du, H.-Y., Kolakowski, Jr., L.F., Lee, A.V., Mandarino, L.J., Fan, J.B., Yee, D. and Liu, F. (1997) Cloning, Chromosome Localization, Expression, and Characterization of an SH2 and PH Domain-containing Insulin Receptor Binding Protein hGrb10 γ . *J. Biol. Chem.*, 272, 29104-29112.
 - c) **Dong, L.Q.**, Porter, S., Hu, D., and Liu, F. (1998) Inhibition of hGrb10 binding to the insulin receptor by functional domain-mediated tetramerization. *J. Biol. Chem.* 273, 17720-17725.
 - d) **Dong, L.Q.**, Landa, L. R., Wick, M.J., Zhu, L., Mukai, H., Ono, Y. and Liu, F. (2000) Phosphorylation of PKN by PDK1 mediates insulin signals to the actin cytoskeleton. *Proc. Natl. Acad. Sci. USA.* 97, 5089-5094.
 - e) Lim, M. A., Kikani, C. K., Wick, M. J., and **Dong, L. Q.** (2003). Nuclear translocation of 3'-phosphoinositide-dependent kinase-1: a potential regulatory mechanism for PDK-1 function. *Proc. Natl. Acad. Sci. USA.* 100, 14006-14011. PMID:14623982.
 - f) Kikani CK, Verona EV, Ryu J, Shen Y, Ye Q, Zheng L, Qian Z, Sakaue H, Nakamura K, Du J, Ji Q, Ogawa W, Sun LZ, **Dong LQ**, Liu F. (2012) Proliferative and antiapoptotic signaling stimulated by nuclear-Localized PDK1 results in oncogenesis. *Science Signaling*, 5(249): ra:80 (PMID: 23131847).
- 2) **Adiponectin signal transduction:** I became a tenure-track Assistant Professor at the University of Texas Health Science Center at San Antonio (UTHSCSA) and set up my own laboratory in 2002. I expanded my research to elucidate adiponectin signal pathway downstream of adiponectin receptors. Since adiponectin receptors (AdipoR1 and AdipoR2) belong to a new family of receptors, investigating the mechanism and regulation of adiponectin signaling have been particularly challenging. In 2006, we have identified an adiponectin receptor binding protein **APPL1**. APPL1, an adaptor protein with multiple function domains, is a signaling molecule with immediate binding to adiponectin receptors, and positively mediate adiponectin signaling to enhance lipid oxidation and glucose uptake in muscle cells. Our subsequent studies have demonstrated that APPL1 acts as an anchoring protein to form a complex with PP2A/PKC δ and clasp LKB1 in the cytosol to activate AMPK in response to adiponectin stimulation. APPL1 also mediates adiponectin-stimulated p38 MAPK activation by scaffolding the TAK1/MKK3/p38 MAPK pathway. Our discovery has been described by peers as “**identifying a novel mechanism linking adiponectin to insulin sensitization**” and “**opening doors to exciting avenues of investigation in adiponectin signaling systems**” (Quoted from a research highlight commentary by Hosch et al, 2006, *Cell Metabolism*, 4, 5-6).
- a) Mao, X., Kikani, C. K., Riojas, R. A., Langlais, P., Wang, L., Ramos, F. J., Fang, Q., Christ-Roberts, C.Y., Hong, J.Y., Kim, R. Y., Liu, F., & **Dong, L. Q.** (2006). APPL1 binds to adiponectin receptors and mediates adiponectin signaling and function. *Nature Cell Biology*. 8, 516-523. (**Highlighted article on cover page**)
Featured in commentary article: Lin, D.C. et al., (2006) APPL1 mechanics: uncovering how adiponectin modulates insulin action. *Cell Metabolism*. 4, 5-6.
 - b) Zhou, L., Deepa, S.S., Etzler, J.C., Ryu, J., Mao, X., Fang, Q., Liu, D.D., Torres, J. M., Jia, W-P., Lechleiter, J.D., Liu, F., & **Dong, L. Q.** (2009). Adiponectin activates AMPK in muscle cells via APPL1/LKB1- and Ca²⁺/CaMKK-dependent pathway. *J. Biol. Chem.*, 284, 22426-22435.
 - c) Deepa, S.S., Zhou, L., Wang, C., Mao, X., Ryu, J., Li, C., Zhang, N., Musi, N., Zhang, B.B., Liu, F., and **Dong, L.Q.** (2011) Adiponectin Stimulates LKB1 Cytosolic Translocation in Muscle Cells through an APPL1-PP2A-PKC δ -dependent Signaling Pathway. *Molecular Endocrinology*. 25: 1773-1785 (PMID: 21835890).
 - d) Xin, X., Zhou, L., Reyes, C.M., Liu, F., and **Dong, L.Q.** (2011). APPL1 mediates adiponectin-stimulated p38 MAPK activation by scaffolding TAK1-MKK3-p38 MAPK pathway. *Am. J Physiol. Endocrinol Metab.*, 300, E103-110 (PMID:20978232).
This paper has been selected as Featured Article on www.MDlinx.com in January 2011).
 - e) Wang, C., Li, X., K. Mu, K., L. Li, L., Wang, S., Zhu, Y., Zhang, M., Ryu, J., Xie, Z., Shi, D., Zhang, W. J., ***Dong, L.Q.**, *Jia, W. (2013) Deficiency of APPL1 in mice impairs glucose-stimulated insulin secretion through inhibition

of pancreatic beta cell mitochondrial function. *Diabetologia*, 56, 1999-2009. (***Corresponding Authors**). (PMID: 23793716).

- 3) **Yin-Yang regulation of adiponectin signaling:** We have reported "Yin-Yang" regulatory mechanism of adiponectin signaling. Since circulating adiponectin concentration is three orders of magnitude higher than most other hormones in humans and is fairly stable throughout the day, it raises an interesting question on how adiponectin signaling is regulated in cells. We have identified **APPL2**, an isoform of APPL1, as another adiponectin receptor binding protein. Interestingly, APPL2 blocks adiponectin signaling in muscle cells, suggesting that APPL1/APPL2 isoforms may act as an integrated "Yin-Yang" regulator of adiponectin signaling. The findings will provide potential mechanisms behind insulin resistance and the development of type 2 diabetes.
- a) Wang, C., Xin, X., Xiang, X., Ramos, F.J., Liu, M., Lee, H-J, Chen, H., Mao, X., Kikani, C.K., Liu, F., and **Dong, L. Q.** (2009). "Yin-Yang" Regulation of Adiponectin Signaling by APPL Isoforms in Muscle Cells. *J. Biol. Chem.*, 284, 31608-31615. (PMID: 19661063).
 - b) Tan, Y., Xin, X., Coffey, F.J., Wiest, D.L., **Dong, L.Q.**, and Testa, J.R. (2015) *Appl1* and *Appl2* are Expendable for Mouse Development but are Essential for HGF-induced Akt Activation and Migration in Mouse Embryonic Fibroblasts. *Journal of Cellular Physiology*, 231(5):1142-1150, PMID: 26445298.
- 4) **Crosstalk between insulin and adiponectin pathways:** We have revealed the molecular mechanisms underlying the crosstalk between adiponectin pathway and insulin pathway. We demonstrate that adiponectin signaling can inhibit lipid-stimulated mTORC1 signaling and prevent insulin resistance in muscle cells. In addition, we identified that phosphorylation of APPL1 at Ser⁴³⁰ mediates ER stress-induced insulin resistance in hepatocytes. Our recent study indicates that the interaction between insulin receptor and IRS proteins is facilitated by adiponectin-stimulated phosphorylation of APPL1 at Ser⁴⁰¹. APPL1 acts as a carrier piggybacking IRS1/2 onto the insulin receptor, which potentiates insulin sensitivity. These studies uncover molecular mechanisms by which APPL1 mediates the cross talk between adiponectin and insulin pathways, and demonstrates that adiponectin is an insulin sensitizer, but not insulin mimic, in cells and *in vivo*.
- a) Wang, C., Mao, X., Wang, L., Liu, M., Wetzell, M., Guan, K-L, **Dong, L. Q.**, and Liu, F. (2007). Crosstalk between adiponectin and insulin signaling pathways: a molecular mechanism for adiponectin as an insulin sensitizer. *J. Biol. Chem.* 282, 7991-7996.
 - b) Holmes, R. M., Yi, Z., De Filippis, E., Berria, R., Shahani, S., Sathyanarayana, P., Sherman, V., Fujiwara, K., Meyer, C., Christ-Roberts, C., Hwang, H., Finlayson, J., **Dong, L.Q.**, Mandarino, L.J., Bajaj, M. (2011) Increased abundance of the adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif (APPL1) in patients with obesity and type 2 diabetes: evidence for altered adiponectin signalling. *Diabetologia*, 54:2122-2131 (PMID: 21562756).
 - c) Tu, Q., Zhang, J., **Dong, L.Q.**, Saunders, E., Tang, J., and Chen, J. (2011). Adiponectin inhibits bone resorption and osteoclastogenesis via APPL1-mediated suppression in Akt1. *J. Biol. Chem.*, 286, 12542-12553, PMID:21300805.
 - d) Liu, M., Zhou, L., Wei, L., Villarreal, R., Yang, X., Hu, D., Riojas, R.A., Holmes, B.M., Langlais, P.R., Lee, H., and **Dong, L.Q.** (2012) Phosphorylation of APPL1 at Ser⁴³⁰ mediates ER stress-induced insulin resistance in hepatocytes. *J. Biol. Chem.*, 287, 26087-26093. (PMID: 22685300).
 - e) Ryu, J., Galan, A.K., Xin, X., Dong, F., Abdul-Ghani, M.A., Zhou, L., Wang, C., Li, C., Holmes, B.M., Sloane, L.B., Austad, S.N., Guo, S., Musi, N., DeFronzo, R.A., Deng, C., White, M.F., Liu, F., and **Dong, L.Q.** (2014) APPL1 Potentiates Insulin Sensitivity by Facilitating the Binding of IRS1/2 to the Insulin Receptor. *Cell Reports*, 7, 1227-1238.

Complete List of Published Work (Total: 70 peer-reviewed articles. H-Index: 31. Publications before 1997 were under the name Dong, Q.):

<http://www.ncbi.nlm.nih.gov/myncbi/collections/mybibliography/>

or

<https://uthscsa.influent.utsystem.edu/en/persons/lily-q-dong>

D. RESEARCH SUPPORT

Ongoing:

R01 DK102965 Dong (PI) 04/01/2015 – 03/31/2020
NIH/NIDDK
The role of TCTP in regulating adiponectin signaling
The goal of this study is to determine the hepatic TCTP in regulating adiponectin signaling, glucose and lipid metabolism, and energy homeostasis.
Role: PI

CTRC Pilot Award Dong (PI) 11/01/2016 – 10/31/2017
Cancer Therapy & Research Center/UTHSA
Identification of key factors in promoting diet-induced NASH and HCC
The major goal of this project is to identify key hepatic factors that trigger diet-induced NASH and HCC.
Role: PI

Pending:

R01 DK115219 Li/Dong (MPI) 7/01/2017 – 6/30/2022
NIH/NIDDK
Regulation of Transcription Elongation in Adipose Homeostasis
Role: PI

17GRNT33700240 Dong (PI) 07/01/2017 – 6/30/2019
American Heart Association/ Association Wide
The role of adipose TCTP in regulating insulin sensitivity
Role: PI

1 P30 DK113677-01 Defronzo (PI) 09/01/2017 – 8/31/2022
NIH/NIDDK
Diabetes Mellitus: Prevention, Treatment, & Cure
Role: Co-Director (Admin-Core) and Core Co-Leader (Core-001)

Completed during past five years:

15GRNT23230035 Dong (PI) 01/01/2015 – 12/31/2016
American Heart Association/ Southwest Affiliate
The role of a novel splicing variant of APPL1 in regulating adiponectin and insulin signaling
Role: PI

#7-13-BS-043 Dong (PI) 7/1/2013 – 6/30/2016
American Diabetes Association-Basic Science Award
The role of APPL2 in regulating insulin sensitivity *in vivo*
Role: PI

R01 DK080344 Dong (PI) 05/01/2009–04/30/2015
NIH/NIDDK
Mechanism of cross talk between insulin and adiponectin signaling pathways

2R56 DK069930-06 Dong (PI) 07/05/2011– 06/30/2013
NIH/NIDDK
Adiponectin signaling and regulation
Role: PI

TTR Award Dong (PI) 6/1/2011-3/31/2013
IIMS/CTSA
Adiponectin signaling and regulation
Role: PI

3R01 DK080344-02S1 Dong (PI) 02/01/2011– 01/31/2013
NIH/NIDDK
The Role of APPL1 in mTORC1 Signaling
Role: PI

Research Projects in Lily Dong Lab (2017)

1. Obesity and type 2 diabetes

Insulin resistance refers to a situation in which insulin target tissues such as liver, skeletal muscle, and fat fail to respond to physiological levels of insulin. It is usually associated with impaired glucose and lipid metabolism, endothelial dysfunction, inflammation, and type 2 diabetes. Although the molecular mechanisms underlying the development of insulin resistance are still unclear, impaired insulin signaling has been proposed to be one of the major causes.

Adiponectin is an adipose tissue-derived hormone with anti-diabetic, and anti-inflammatory functions. Reduced adiponectin levels and action are associated with obesity and type 2 diabetes. On the other hand, increased adiponectin signaling and action reduces diet-induced obesity, inflammation, insulin resistance, cardiovascular diseases, and type 2 diabetes, suggesting a promising therapeutic approach for the treatment of obesity-associated metabolic and type 2 diabetes. However, the molecular mechanisms underlying adiponectin action remain largely unknown. Our laboratory identified for the first time an adiponectin receptor interactive protein, APPL1, which plays an essential role in adiponectin signaling. Subsequently, we showed that APPL2, an isoform of APPL1, acts as integrated Yin-Yang regulatory machinery with APPL1 to regulate adiponectin signaling in cells. Our current projects aim to elucidate the mechanisms by which APPL isoforms regulate adiponectin signaling. Since impairment of adiponectin signaling together with reduced level of adiponectin in obesity and type 2 diabetes play important roles in development of insulin resistance, understanding the mechanisms underlying adiponectin signaling regulation may lead to identification of novel and effective therapeutic strategies for the prevention and treatment of metabolic disorders.

2. Liver Cancer

Hepatocellular carcinoma (HCC) is a serious disease in human adults. It is well established that over-nutrition promotes non-alcoholic fatty liver disease (NAFLD, also called simple steatosis), a reversible stage that could either be recovered back to normal, or further developed to nonalcoholic steatohepatitis (NASH), a situation in which severe fat accumulation in the liver accompanied with inflammation. Once the liver is at the NASH stage, it can be induced irreversibly to cirrhosis and HCC under certain pathology conditions.

Recent reports indicate that type 2 diabetes, obesity, and NASH are associated with the growing incidents of cirrhosis and HCC in Texas Hispanic population, suggesting that insulin resistance, fatty liver, and chronic inflammation could be the risk factors for pushing NAFLD to NASH, leading to HCC. However, it remains unclear whether and how insulin resistance, fatty liver, and chronic inflammation are sufficient to trigger the diet-induced switch from NAFLD to NASH. With the unique animal models generated from our lab, we aim to identify key factors that are responsible for HCC initiation and development under over-nutrition conditions. Completion of this project will provide valuable information on the mechanism by which over nutrition-induced liver diseases including HCC.